pending claim 1, original claim 20 and at pages 21-22 of the specification. No new matter is added by such amendments to claim 19.

Elections/Restrictions

The Examiner states that "[u]pon consideration of Applicant's arguments, Group I, Species 1 (claims 1-12 and 19) and Group II, Species 1 (claims 20-21) are rejoined and will be examined together." Applicant wishes to clarify the characterization of the Group and Species of each of the pending claims. At page 4 of Paper No. 8 (Office Action dated September 8, 2000), the Examiner stated that claims 1-9 and 19 were generic. The Examiner then defined four "patentably distinct species of the claimed invention." The four species, defined by the mathematical solution to the residence time, were: "1) the solution as claimed in claim 10; 2) the solution as claimed in claim 13; 3) the solution as claimed in claim 15; and 4) the solution as claimed in claim 18." Applicant submits that claims 20 and 21, like claims 1-9 and 19, are generic. The remaining claims of restriction Group II, claims 22-24 determine the residence time in the same manner as claim 15. Therefore claims 22-24 would properly be classified as Group II, Species 3. Although the Examiner has withdrawn claims 22-24 from consideration, Applicant reserves the right to present the species embodied in claims 22-24 upon allowance of a generic claim.

Accordingly, claims 1-9 and 19-21 are generic claims of the elected, rejoined Groups I and II. Claims 10-12 are the elected Species 1. Applicants reserve the right to present the claims embodying Species 2 (claims 13-14), Species 3 (claims 15-17 and 22-24) and Species 4 (claim 18) upon allowance of a generic claim.

35 U.S.C. §112, first paragraph

The Examiner has rejected claim 19 under 35 U.S.C. §112, first paragraph, as containing subject matter with inadequate description in the specification.

The test for written description is whether the applicant "convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1119 (Fed. Cir. 1991). The Examiner asserts that "[w]ith the exception of a calculated optimal dosage of ^{131}I-labeled anti-B1 radiopharmaceutical, the skilled artisan cannot envision the

optimal dosage of any radiopharmaceutical, regardless of the complexity or simplicity of the method of derivation." The Examiner further avers that the "dosage of each radiopharmaceutical itself is required."

In support of the rejection, the Examiner points to several cases relating to patents in the field of molecular biology, drawn in particular to DNA. The present invention, however, is not related to DNA or molecular biology. The present invention is directed instead to an optimally effective dose of a radiopharmaceutical and methods of obtaining such a dose. The methods and products of the instant invention concern radioisotopes and radiopharmaceuticals. The behavior of radioisotopes and pharmaceuticals, with reference to the various parameters taught by the Applicant and how to account for variability in a given case, is more predictable than a generally described nucleic acid or the field of molecular biology in general.

One of skill in the art would be capable of obtaining an optimally effective therapeutic dose for a radiopharmaceutical of interest by performing each of the steps of claim 19. For example, one of skill in the art would be able to determine the maximum tolerated dose for any pharmaceutical regardless of whether it is radiolabeled or not. The determination of maximum tolerated dose is described in detail at page 7, line 20, to page 8, line 28. One of skill in the art would also have the knowledge necessary to determine the desired total body dose of the radiopharmaceutical for the patient. A detailed discussion of the desired total body dose occurs at page 9, lines 1-31 of the specification. Further, clearance profile refers to a general characteristic of any radiopharmaceutical. A practitioner would have several ways in which to determine the clearance profile, as discussed in detail at page 10, line 2, to page 12, line 3. In particular, Applicant wishes to call the Examiner's attention to the fact that the clearance profile may even be available in historical sources such as published literature. Therefore one of skill in the art would be able to determine the clearance profile of any radiopharmaceutical, not just ^{131}I-labeled anti-B1. Additionally, determining the patient's mass and maximum effective mass is completely independent of the radiopharmaceutical used and the specification provides adequate written description for this aspect of the invention, particularly at page 12, line 5, to page 14, line 17. The value for activity hours is based on both patient-specific and radionuclide-specific characteristics, but Applicant provides a clear formula

that is applicable to any radiopharmaceutical for determining this value. A clear description of determining activity hours in a given case can be found at page 14, line 19, to page 18, line 9. Finally, the specification provides an extensive discussion of methods of determining residence time, particularly through the use of an administered tracer dose, at page 18, line 11 to page 25, line 11. In this discussion, several formulas and graphical methods for calculating this value are provided by the specification. There is nothing in these formulas that limit them simply to ^{131}I-labeled anti-B1 or even to ^{131}I-labeled pharmaceuticals. Accordingly, Applicant submits that the specification clearly conveys to one of skill in the art that the inventors had possession of the invention of claim 19. Methods for establishing patient-specific optimally effective doses for administration of radiopharmaceuticals and doses so established were well within their possession, regardless of the radionuclide or radiopharmaceutical at issue.

Indeed, one case upon which the Examiner relied, *University of California v. Eli Lilly and Co.*, supports the adequacy of the present written description with its holding that:

> [A]n applicant complies with the written description requirement by describing the invention with all its claimed limitations, not that which makes it obvious, and by using such descriptive means as words, structures, figures, diagrams, *formulas*, etc. that set forth the claimed invention.

In the present case, Applicant provides explicit formulas, applicable to many different radiopharmaceuticals. Thus, the present claims fulfill the written description requirement.

The remaining cases cited by the Examiner do not apply. *Fiers v. Revel* and *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.* refer to the relatively unpredictable field of molecular biology. *Fiddes v. Baird* deals with claiming broad classes of genes based on the limited description of a single gene. Molecular biology is recognized by the Federal Circuit to be an unpredictable science. The present invention, however is essentially a matter of physics, the measuring of physical characteristics, including within a patient environment, and application of specific formulas. Each of these is predictable to a great extent or otherwise accounted for in the teachings, as by how to tailor the appropriate dose depending on a given residence time. Accordingly, Applicant submits

that the specification adequately supports an optimal dose of any radiopharmaceutical determined by the method of the invention and respectfully request that the Examiner withdraw the 35 U.S.C. §112, first paragraph rejection.

35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1-12 and 19-21 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is amended to refer to "a clearance profile," and to delete reference to "the" before "activity hours" and "residence time" the first time each term appears in independent claim 1.

The Examiner notes that the final step of Claims 1 and 19 is establishing the "optimally effective dose" by solving an equation for "therapeutic dose." The Examiner states that "it is not clear if the 'therapeutic dose' of claims 1 and 19 is the same as the 'optimally effective dose'." The therapeutic dose, as determined by solving the equation, is the optimally effective dose.

Claim 4 is amended to delete "the" from before "lean body mass."

Claim 19 is amended to refer to "a clearance profile," and to delete reference to "the" before "activity hours" and "residence time" the first time each term appears in independent claim 19. Claim 19 is further amended as previously described to bring it in conformity with claim 1.

The reference to Equation 1 at line 12 of claim 20 is a typographical error. Claim 20 is amended to refer only to Equation I. Claim 20 is further amended to delete reference to "the" before "activity hours" at the first instance of this term in independent claim 20.

Claim 21 is amended to refer to "a clearance profile". The "residence time" in claim 21 refers back to the patient-specific residence time of claim 20. Claim 21 is further amended to refer to "the patient-specific residence time" to emphasize that the residence time refers directly back to the residence time determined in claim 20.

Applicant submits that the claims, as amended, particularly point out and distinctly claim the subject matter which Applicant regards as the invention and thereby

satisfy the requirements of under 35 U.S.C. §112, second paragraph. Accordingly, Applicant requests the Examiner to withdraw the rejection under 35 U.S.C. §112, second paragraph.

35 U.S.C. §102

The Examiner has rejected claim 19 under 35 U.S.C. §102 as being anticipated by Order (1980).

The Examiner states that "a product by process claim is examined for novelty and obviousness of the claimed product only, and that no consideration is given to the novelty or obviousness of the method of making the claimed product." The Examiner avers that Order "teaches a therapeutically effective dose of a radiopharmaceutical in a patient and demonstrates the optimal therapy of intrahepatic malignancies with radiolabelled antibodies." Indeed, the article does disclose a therapeutically effective dose. However, claim 19 is drawn to an *optimally* effective therapeutic dose of a radiopharmaceutical for administration to a patient. The present invention is a dosage that is optimized to each particular patient. As discussed in the Background section of the specification, at pages 1-2, conventional methods do not take into account the substantial variance among patients in how long radiopharmaceuticals are retained in the body. Indeed, the Order article describes the one patient who experienced toxicity as having "a prolonged retention of radioactivity (effective half-life of 5.6 days)." The effective half-life of the radiolabeled antibody ranged from 1.7 to 4.3 days in the other patients. Clearly, Order was not providing an optimal dose based on the individual characteristics of each patient. Therefore, Applicant submits that the patient-specific optimal dose of the present invention is not the same as the standard dose administered to the patients described in Order, et al. and requests the Examiner to withdraw the rejection.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made."

In view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (415) 693-2120.

Cooley Godward LLP
Attn: Patent Group
Five Palo Alto Square
3000 El Camino Real
Palo Alto, CA 94306-2155
Tel: (650) 893-5000
Fax: (650) 857-0663
GKS:KEF:sb

Attachment

Respectfully submitted,
COOLEY GODWARD LLP

By: Gurjeev K. Sachdeva
Gurjeev K. Sachdeva
Reg. No. 37,434

Version with markings to show changes made

1. (Amended) A method of establishing a patient-specific optimally effective dose for administration of a radiopharmaceutical to a patient, the method comprising:

determining a maximum tolerated dose for the radiopharmaceutical;

determining a desired total body dose of the radiopharmaceutical for the patient;

determining ~~the~~ a clearance profile for the radiopharmaceutical or a radiopharmaceutical analog;

determining the patient's mass and maximum effective mass;

selecting the lower of the patient's mass and maximum effective mass;

determining ~~the~~ activity hours for the radiopharmaceutical or radiopharmaceutical analog based on the lower of the patient's mass or maximum effective mass and the desired total body dose;

determining ~~the~~ residence time of an administered tracer dose of the radiopharmaceutical or the radiopharmaceutical analog in the whole body of the patient, the residence time being correlated to the clearance profile; and

establishing the optimally effective dose of the radiopharmaceutical for the patient by solving for therapeutic dose in the following equation:

$$\text{therapeutic dose} = \frac{\text{Activity Hours}}{\text{Residence time}} \times \frac{\text{desired total body dose}}{\text{maximum tolerated dose.}}$$

2. (Reiterated) The method of claim 1, wherein the step of determining the maximum tolerated dose comprises performing a dose escalation study for the radiopharmaceutical in a patient population.

3. (Reiterated) The method of claim 1, wherein the maximum effective mass is based on the radiopharmaceutical.

4.(Amended) The method of claim 1, wherein the maximum effective mass is correlated to ~~the~~ lean body mass of the patient.

5. (Reiterated) The method of claim 1, wherein the maximum effective mass is based on the gender and height of the patient.

6. (Reiterated) The method of claim 1, wherein the step of determining the clearance profile comprises performing a study following measurement over time of the loss of radioactivity from an administered radiopharmaceutical.

7. (Reiterated) The method of claim 1, wherein the step of determining the clearance profile comprises performing a dose escalation study for the radiopharmaceutical.

8. (Reiterated) The method of claim 1, wherein the clearance profile provides an activity-time curve shape for the radiopharmaceutical.

9. (Reiterated) The method of claim 1, wherein the clearance profile provides an indication of the number of exponential terms in the function defining the pattern of clearance for the radiopharmaceutical.

10. (Reiterated) The method of claim 1, wherein the step of determining the residence time for the radiopharmaceutical comprises:

making measurements of radioactivity in the whole body of the patient at each of a number of time points,

calculating percent injected activity of the radiopharmaceutical at each of the time points, and

establishing the residence time by plotting the time points vs. percent injected activity on a semilog graph and determining 37% injected activity.

11. (Reiterated) The method of claim 10, wherein each time point is background corrected.

12. (Reiterated) The method of claim 10, wherein the number of time points are correlated to the clearance profile of the radiopharmaceutical so that at least 2

measurements are made if the radiopharmaceutical has monoexponential clearance, at least 4 measurements are made if the radiopharmaceutical has biexponential clearance, and at least 6 measurements are made if the radiopharmaceutical has triexponential clearance.

19. (Amended) An optimally effective therapeutic dose of a radiopharmaceutical for administration to a patient, said optimally effective therapeutic dose determined by the method comprising:

determining a maximum tolerated dose for the radiopharmaceutical ~~for the patient population~~;

determining a desired total body dose of the radiopharmaceutical for the patient;

determining ~~the~~ a clearance profile for the radiopharmaceutical or a radiopharmaceutical analog;

determining the patient's mass and maximum effective mass;

selecting the lower of the patient's mass and maximum effective mass;

determining ~~the~~ activity hours for the radiopharmaceutical or radiopharmaceutical analog based on the lower of the patient's mass or maximum effective mass and the desired total body dose;

~~administering a tracer dose of the radiopharmaceutical or the radiopharmaceutical analog to the patient;~~

determining ~~the~~ residence time ~~for the~~ of an administered tracer dose of the radiopharmaceutical or the radiopharmaceutical analog in the whole body of the patient, the residence time being correlated to the clearance profile; and

establishing the optimally effective dose of the radiopharmaceutical for the patient by solving for therapeutic dose in the following equation:

$$\text{therapeutic dose} = \frac{\text{Activity Hours}}{\text{Residence time}} \times \frac{\text{desired total body dose}}{\text{maximum tolerated dose.}}$$

20. (Amended) A method of establishing a patient-specific optimally effective dose for administration of a radiopharmaceutical to a patient, the method comprising:

determining the desired total body dose (TBD) of the radiopharmaceutical for the patient;

determining the patient's mass (M) and maximum effective mass (MEM);

selecting the lower of the patient's mass and maximum effective mass (M or MEM);

determining ~~the~~ activity hours (AH) for the radiopharmaceutical or a radiopharmaceutical analog by reference to Equation I:

$$AH = \frac{TBD \times (M \text{ or } MEM)}{\left[\sum_{elec} \Delta_{elect} + \sum_{phot} \Delta_{phot}\, \phi^{TB}_{phot}\right]}$$

(Equation I)

where $\left[\sum_{elec} \Delta_{elect} + \sum_{phot} \Delta_{phot}\, \phi^{TB}_{phot}\right]$

in Equation ~~I~~ I represents the sum of electron energy and photon energy deposited in the total body of the patient by the radiopharmaceutical or radiopharmaceutical analog;

determining the patient-specific residence time of an administered tracer dose of the radiopharmaceutical or the radiopharmaceutical analog in the whole body of the patient;

and

establishing a therapeutic dose of the radiopharmaceutical for the patient by dividing the activity hours by the patient-specific residence time to obtain a value and optionally multiplying the value by an attenuation factor, said attenuation factor being determined by the TBD divided by the maximum tolerated dose for the radiopharmaceutical.

21. (Amended) The method of claim 20 further comprising the step of determining ~~the~~ a clearance profile for the radiopharmaceutical or the radiopharmaceutical analog, said clearance profile providing a minimum number of time points for determination of

the patient-specific residence time of the radiopharmaceutical or the radiopharmaceutical analog.

83. (New) The method of claim 1 wherein the radiopharmaceutical is an ^{131}I-labeled anti-B1 antibody.

84. (New) The method of claim 19 wherein the radiopharmaceutical is an ^{131}I-labeled anti-B1 antibody.